UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,141	07/24/2003	Srinivas G. Rao	CYPR 101	5413

7278 7590 04/03/2007

DARBY & DARBY P.C.
P. O. BOX 5257
NEW YORK, NY 10150-5257

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/628,141	RAO ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10-14 and 19-21* is/are pending in the application.

4a) Of the above claim(s) *11,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10,12-14 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 1/18/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election/Restrictions

Newly submitted claims 20-21 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly submitted claims require the administration of milnacipran in combination with one or more active compounds. However, the originally claimed invention is only drawn to the administration of an NSRI or TRI. As such, the newly submitted claims introduce limitations not required by the originally claimed invention and would require a different search.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 20-21 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Status of the Claims

Claims 1-7, 10-14 and 19-21 are currently pending and are the subject of this Office Action. Claims 1 and 14 are presently amended and claims 19-21 are newly presented. Claims

11 and 20-21 are withdrawn from consideration. Claims 1-7, 10-14 and 19 are presently under examination.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 1/18/2007 was filed after the mailing date of the Non-Final Office Action on 10/4/2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Please see attached USPTO Form 1149.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7, 10 and 12-13 rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Applicant's arguments filed 1/18/2007 have been fully considered but are not persuasive. Firstly, it is noted that Applicants have amended claim 14 to recite the compounds explicitly named at pages 10-13 of the specification (namely milnacipran, bicifadine, sibutramine, venlafaxine and duloxetine). In view of this amendment, claim 14 has been removed from this

rejection. However, claim 1 still recites "a dual norepinephrine serotonin reuptake inhibitor (NSRI) or a triple reuptake inhibitor (TRI)" generally. With respect to the recitation of an "aminocyclopropane derivative" in claim 10, Applicants argue that "aminocyclopropane" clearly suggests what structural features are present, namely a cyclopropane group and an amino substituent. Applicants further argue that suitable aminocyclopropane derivatives are described in U.S. Patent Nos. 5,621,142 and 4,478,836, which are both incorporated by reference. This argument is persuasive only for those aminocyclopropane compounds represented by the structures disclosed in the '142 and '836 patents. However, Examiner respectfully maintains that "aminocyclopropane derivative" is not adequately described in the specification. There are literally hundreds of thousands, if not millions, of possible compounds encompassed by the limitation "aminocyclopropane derivative". Reference to two specific chemical formulas comprising aminocyclopropanes does not provide an adequate description of the broadly claimed genus.

The claims are drawn to "a dual norepinephrine serotonin reuptake inhibitor (NSRI) or a triple reuptake inhibitor (TRI)". Claim 10 recites an "aminocyclopropane derivative". The specification discloses examples of preferred compounds of the invention (*e.g.*, pages 10-13), which include milnacipran, bicifadine, sibutramine, venlafaxine and duloxetine. The specification also refers to two U.S. Patents (5,621,142 and 4,478,836) with respect to suitable aminocyclopropane derivatives. The specification does not disclose any other specific NSRIs, TRIs or aminocyclopropane derivatives as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus.

The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claims is a recitation of "a dual norepinephrine serotonin reuptake inhibitor (NSRI) or a triple reuptake inhibitor (TRI)" or an "aminocyclopropane derivative". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to the DNA arts, the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe Inc.* are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *Lilly*. The court stated that, "[A] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " *Lilly* at 1567, 43 USPQ2d at 1405. The court also stated that:

> "[A] generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." *Id.* at 1568, 43 USPQ2d at 1406.

The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." *Id.*

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.*

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The *Enzo* court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324, 63 USPQ2d at 1613 (emphasis added, bracketed material in original).

While the inventions at issue in *Lilly* and *Enzo* were DNA constructs *per se*, the holdings of those cases are also applicable to claims such as those at issue here (which are drawn to active agents only defined by activity). The instant specification may provide an adequate written description of NSRIs or TRIs, per *Lilly*, by structurally describing representative inhibitors (*e.g.*, specific compounds, compound formulas, etc.), or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per *Enzo*, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics

when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe NSRIs or TRIs useful in the claimed invention in a manner that satisfies either the *Lilly* or *Enzo* standards. Although the specification discloses five specific inhibitors, this does not provide a description of the broadly claimed NSRIs, TRIs or aminocyclopropane derivatives that would satisfy the standard set out in *Enzo* because the specification provides no functional characteristics coupled to structural features (*i.e.*, what structural features, for example, impart NSRI or TRI activity). Further, the specification also fails to describe NSRIs, TRIs or aminocyclopropane derivatives by the test set out in *Lilly* because the specification describes only five specific compounds. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of NSRIs, TRIs or aminocyclopropane derivatives that is required to practice the claimed invention.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1-7, 10, 12-14 and 19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mouzin *et al.* (U.S. Patent No. 4,478,836) in view of Moret *et al.* (1985) and Ruoff (1996).

Applicant's arguments filed 1/18/2006 have been fully considered but they are not persuasive. Applicants argue, *inter alia*, that Ruoff teaches away from the claimed methods because the reference discloses that the norepinephrine serotonin reuptake inhibitor (NSRI), venlafaxine, is associated with serious side effects. As such, applicants assert that one skilled in the art would not be motivated to administer a NSRI to treat depression secondary to pain (DSP). Applicants further argue that Ruoff discloses that tricyclic antidepressants are considered second or third-line therapy when compared to the newer antidepressants. These arguments are not persuasive. Examiner respectively submits that the prior art: 1) teaches all of the claimed limitations; 2) provides ample motivation to combine Mouzin *et al.*, Moret *et al.* (1985) and Ruoff (1996); and 3) provides the skilled artisan with at least a reasonable expectation of success. The fact that venlafaxine is associated with side effects does not teach away from the claimed methods. This is only one example of an NSRI that happens to be associated with side effects. For example, the NSRI milnacipran has been used to treat depression for years with minimal side effects. Thus, one skilled in the art would recognize that NSRIs can be safely administered to treat depression. Mouzin *et al.* ('836 patent) disclose that milnacipran, salts of milnacipran, and derivatives thereof are useful in the treatment of depression (see especially Abstract). Moret *et al.* disclose that milnacipran is a dual norepinephrine (NE) serotonin (5-HT) reuptake inhibitor (see especially Abstract), has a NE:5-HT reuptake inhibition ratio of 2:1

(Table 4, page 1215), and can be used to treat depression at a dose of 50 mg twice a day (page 1218, last paragraph). Thus, Mouzin and Moret provide motivation to treat depression with the NSRI, milnacipran. Neither Mouzin *et al.* nor Moret *et al.* specifically teach the treatment of DSP with a NSRI. However, it is noted that DSP is a subtype of depression, characterized by the fact that it is generally observed in patients with chronic pain. One skilled in the art would have been imbued with at least a reasonable expectation that drugs suitable to treat depression would also be effective in treating DSP. This is especially true given the teachings of Ruoff.

Ruoff discloses that the neurotransmitters serotonin and norepinephrine have been implicated in both perception of pain and the pathogenesis of depression and that antidepressants have been shown to be effective in the treatment of a variety of chronic pain syndromes, including peripheral neuropathic pain, headache, migraine, facial pain, fibrosis, and rheumatic pain (page S27). The reference further states that, "Regardless of whether depression is secondary to the pain syndrome or is the primary condition, the mood disorder should be thoroughly assessed and treated pharmacologically" (page S28, "Treatment Approaches"). Ruoff further discloses that the NSRI antidepressant, venlafaxine, exerts its antidepressant activity through selective inhibition of norepinephrine and serotonin uptake (Page S30, "Venlafaxine"). Thus, the reference provides further motivation to treat depression with an NSRI.

As noted by the Applicants, the relationship between chronic pain and depression is complex and not entirely understood. However, the treatment of depression secondary to pain is suggested by the reference to be the same as that for treatment of other types of depression. Ruoff states on Page S32, last paragraph that: "Clinicians must carefully assess patients prior to initiating antidepressant therapy. However, once depression is diagnosed, treatment in the patient

with chronic pain is no different than in patients without pain. Antidepressant therapy should be started early and in full doses." Clearly, this statement, and in fact the entire disclosure of Ruoff, provides ample motivation to treat DSP with NSRIs. Ruoff explicitly states that the treatment of depression in patients with chronic pain (*i.e.* depression secondary to pain) is no different than treating other types of depression. As such, the skilled artisan would have been motivated to treat DSP with known antidepressants, including the NSRI taught by Mouzin and Moret.

Examiner respectfully maintains that the instantly claimed methods of treating DSP with NSRIs would have been *prima facie* obvious given the known use of the NSRI milnacipran to treat depression. In addition, the prior art is clear with regard to the relationship between pain and depression; as Applicants have previously stated in their arguments, the relationship is complex and not entirely understood. However, it is the diagnosis of depression in patients having chronic pain that is complex. Once that diagnosis has been properly made, the treatment is, as suggested by Ruoff, no different than that used for depression without pain. In fact, at the time the invention was made, the prior art made no distinction in the treatment of depression and atypical depression secondary to pain.

Thus, Claims 1-7, 10 and 12-13 would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art. This is especially true given that milnacipran was known in the art to be a dual norepinephrine serotonin uptake inhibitor useful in the treatment of depression due to its minimal side effects. The drug had been used, in the doses instantly claimed, to treat major depression (Moret *et al.*, page 1218). Lastly, Ruoff explicitly states that the treatment of depression in a patient having chronic pain is no different than in patients without pain. As such, the skilled artisan would be motivated to treat DSP with any

antidepressant, including the NSRI milnacipran as taught by Mouzin *et al.* and Moret *et al.* and would have been imbued with at least a reasonable expectation that such treatment would be effective.

Claim 10 was inadvertently left out of the previous rejection. Thus, with respect to claim 10, it is generally obvious to combine two active agents, each of which is individually known to be useful in the treatment of the same condition. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said agents flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960). Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself. The natural presumption that two individually known antidepressant agents would, when combined, provide a third composition also useful for treating depression flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption. Thus, the fact that milnacipran has been used to treat depression and sibutramine has the same mechanism of action, it follows that a combination of the two agents would also be effective in treating depression.

Upon further consideration claims 14 and 19 are now also rejected. The limitation wherein the DSP is "characterized by mood reactivity and neurovegetative symptoms present for more than two weeks" fails to distinguish the claimed methods from the prior art. It is not clear that this patient population is different from other patient populations having DSP. Further, as noted above, it would have been obvious to treat <u>any</u> form of depression with milnacipran given its use in the treatment of major depression.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

March 23, 2007

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER

3/28/07